Remarks

Claims 1-9, 12-23 and 27-30 are pending in the subject application. Applicants acknowledge that claims 20-23, 27 and 28 have been withdrawn from further consideration as being drawn to a non-elected invention. Accordingly, claims 1-9, 12-23 and 27-30 are currently before the Examiner and claims 1-9, 12-19 and 29-30 read on the elected invention. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the objections to the specification and the rejections under 35 U.S.C. § 112, first paragraph.

Upon consideration of the arguments presented herein, Applicants respectfully request the courtesy of an interview to discuss the rejection of record and this response to that rejection.

Claims 1-9 and 12-19 remain rejected under 35 U.S.C. § 112, first paragraph, as noncnabled by the subject specification. The Office Action indicates that the specification is enabled for method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-881)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, but is not enabled for method for producing any other heterodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein any and all domains of the TCR-complex has been modified by mutagenesis to obtain the sterically arranged groups on TCR chains. Applicants respectfully assert that the claims are enabled and traverse the rejection of record.

The Office Action argues that the previously submitted arguments were not found persuasive for the following reasons (see the paragraph bridging pages 3-4 of the Office Action dated March 6, 2009):

> The scope of the instant claims encompasses method for producing any hetrodimeric specific wild-type or chimeric TCR with any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-complex has been modified by mutagenesis and the functionality and stability of the TCR is maintained. Although it was known how to make mutated TCRs, how to introduce them into cells and how to test TCR functionality, the state of the art at the time of filing was such that the TCR is the most intricate membrane receptor structures known in the art, wherein any mutation

> in the TCR-complex would cause unintentional conformational changes rendering the scope of invention as claimed highly unpredictable. It was unpredictable at the time of the invention whether the mutations, including reciprocal exchange, introduced to various TCR domains, including extracellular domain, variable domain, constant domain, connecting peptides, transmembrane domain and intracellular domain, would be able to maintain TCR functionality and stability. In instant case producing wild-type or chimeric TCR receptors specific to a particular antigen and to maintain its functionality and stability, wherein the first and second chain mutated to provide sterically arranged sites is not considered routine in the art and without sufficient guidance to a specific TCR structure associated with corresponding mutated sites designated on each TCR chain, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

With respect to these reasons for maintaining the rejection of record, Applicants note that the scope of the claims does not encompass the modification of "any and all domains (*i.e.*, extracellular, transmembrane and intracellular domains) of the TCR-complex" by mutagenesis such that "the functionality and stability of the TCR is maintained". Rather, the claims indicate that a "surface" on a first and second chain are mutagenized in a manner that allows for the introduction of sterically projecting and sterically recessed groups into each respective polypeptide chain (see claim 1, lines 6-9 and 14-27) such that TCR functionality and stability is not impaired. As noted in the as-filed specification (at pages 6-7), a "surface" is the area of a TCR that interacts with a particular area of the second chain of the TCR. Applicants further note that the crystal structure of the T cell receptor had been resolved at the 2.5 Angstrom level and that the various "surfaces" that interact with one another were known at the time the instant application was filed (see Garcia *et al.*, *Science*, 1996, 274:209-219, for example, pages 213-214, "The Cα-Cβ interface" and "Elbow region", a copy of which is attached to this response for the convenience of the Examiner). Applicants further note that the as-filed specification contains teachings as to those amino acid residues suitable for mutagenesis and provides a great deal of teaching as to how one can practice the claimed invention, including amino acid residues suitable for mutagenesis (see pages 28-34, particularly pages 29-31). Thus, and contrary to the assertion made in the Office Action, Applicants submit that one skilled in the art would not have had to engage in undue and extensive experimentation in order to practice the claimed invention.

Applicant also notes that the Office Action argues that the claims fall "in the realm of gene therapy" and that the state of the art, with respect to gene therapy *in vivo*, was unpredictable. The Office Action argues that the greatest challenge in this area was the efficient transfer and stable expression of a transgene in a target tissue. As discussed in Ogris *et al.* (*DDT*, 2002, 7(8):479-485), a copy of which is attached to this response for the convenience of the Examiner, a number of targeted non-viral nucleic acid delivery systems were known to those skilled in the art at the time the claimed invention was made. For example, delivery systems that utilized nucleic acid condensing agents and targeting agents, such as antibodies, existed. The delivery system condensing agents could be separated into two classes—polycationic lipids and polycationic molecules. Both classes of condensing agents (polycationic carriers) reduce the dimensions of the nucleic acids associated with the polycationic compounds and also protect the nucleic acids from nucleases. Exemplary polycationic carriers discussed in the reference include polycationic lipids, polycationic proteins such as histones or protamines, chemically synthesized compounds such as the poly-amino-acids, polylysine, polyarginine or polyhistidine or polyethylenimine (PEI) (see page 481, column 1, paragraphs 1-2).

Ogris *et al.* further indicate that strategies existed for reducing non-specific interactions of the polycationic carrier/nucleic acid complex with blood components and to enable the circulation of complexed DNA in the bloodstream. These strategies included "shielding" the complex surface with hydrophilic polymers, such as (poly)ethylene glycol (PEG), (poly)hydroxypropylmethacrylamide (pHPMA) or (poly)vinylpyrrolidine (see page 481, column 1). Ogris *et al.* further teach that the non-viral drug delivery systems discussed can be actively targeted to specific cells via a variety of targeting agents (including transferrin, EGF and antibodies specific for cell surface markers (page 481, column 2)). Thus, it is clear that one skilled in the art would have been able to direct nucleic acids within the scope of the claimed invention to T cells *in vivo* without undue experimentation in view of the state of the art at the time the invention was made. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

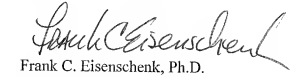
Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/sl
Attachments: Copy of Garcia *et al.*, 1996
Copy of Ogris *et al.*, 2002